PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003380	15.10.2004	17.10.2003

International Patent Classification (IPC) or both national classification and IPC
C12N1/20, C12P17/18, A61K31/535, C12R1/465

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

van de Kamp, M

Telephone No. +31 70 340-2373

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/003380

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	18-20
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	18-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement (Continuation)

2.1 CITATIONS

Reference is made to the following documents:

D1: US-A-5 194 378 (SALITURO ET AL) 16 March 1993

D1 was cited in the application.

2.2 NOVELTY (Art. 33(2) PCT)

2.2.1 The present application does not meet the requirements of Article 33(1) PCT, because the subject-matter of **claims 18-20** is not new in the sense of Article 33(2) PCT.

2.2.2 **D1** discloses tacrolimus characterised as an immunosuppressant (e.g., Ex. 2), further referring to US4894366 with respect to its usefulness in medical treatment and prevention of transplantation rejection of organs or tissues (column 7 line 63-column 8 line 2). It is unclear wherein tacrolimus of the current application differs from tacrolimus as disclosed in **D1**, thus rendering **claims 18-20** not novel.

2.2.3 The subject-matter of **claims 1-17** can be recognised as new in the sense of Article 33(2) PCT, since the prior art as cited does not disclose the use of *Streptomyces glaucescens* MTCC 5115 as a tacrolimus-producing microorganism

2.3 INVENTIVE STEP (Art. 33(3) PCT)

2.3.1 **D1** is regarded as being the closest prior art to the subject-matter of independent **claims 1-3** and discloses an isolated microorganism *Streptomyces*

sp. ATCC 55098 (MA6858), and a fermentation process for producing tacrolimus (FK-506, FR-900506) using said strain. Yields are approx. 35 microgr/ml (column 9 line 38-44). The subject-matter of **claims 1-3** differs particularly in that a different strain with different characteristics (Table 1-3) is referred to. Tacrolimus yields with the strain of the current application, *Streptomyces glaucescens* MTCC 5115, are in the range of 5-10 microgr/ml (Ex. 4).

2.3.2 The problem to be solved by the subject-matter of **claims 1-3** may therefore be regarded as providing an alternative fermentative process for producing tacrolimus, as well as an alternative microorganism which can be used in such a process. The solution would be the use of the *S. glaucescens* strain as said in a fermentative process for producing tacrolimus.

2.3.3 This solution can be considered as involving an inventive step (Article 33(3) PCT) for the reasons that it is not considered to be obvious to the skilled person to embark upon a program to isolate alternative tacrolimus-producing strains, or even when this would be considered obvious that such a program would yield the *S. glaucescens* MTCC 5115 strain of the current invention with characteristics as outlined in Table 2 and 3.

2.3.4 The present application does therefore satisfy the criterion set forth in Article 33(3) PCT insofar as the subject-matter of **claims 1-17** involve an inventive step (Rule 65(1)(2) PCT).

2.4 INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

2.4.1 The subject-matter of **claims 1-20** satisfies the criterion set forth in Art. 33(4) PCT in conjunction with Rule 5.1(a)(vi) PCT with respect to industrial applicability.

2.4.2 For the assessment of the present **claims 18 and 19** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the

claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. For the present purpose, **claims 18 and 19**, although directed to a method of treatment of the human/animal body, have been considered as referring to the effects of the compound/composition which can be used in a method of treatment or prevention.

Re Item VIII

Certain observations on the international application (Continuation)

1 CLARITY (Art. 6 PCT)

1.1 In **claim 15** the words 'steps of' seem to be missing between '...one or more' and 'of filtration...'.